

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 August 2003 (07.08.2003)

PCT

(10) International Publication Number
WO 03/063873 A1

- (51) International Patent Classification⁷: **A61K 31/519**, A61P 13/10 (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).
- (21) International Application Number: PCT/GB03/00374 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 29 January 2003 (29.01.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 0202265.5 31 January 2002 (31.01.2002) GB (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): ARACHNOVA THERAPEUTICS LTD. [—/—]; 95 Halkett Place, St. Helier, Jersey JE1 1BX (GB).
- (72) Inventors; and (75) Inventors/Applicants (*for US only*): CAVALLA, David [GB/GB]; Arachnova Ltd., St. John's Innovation Centre, Cambridge CB4 0WS (GB). GRISTWOOD, Robert, William [GB/GB]; Arachnova Ltd., St. John's Innovation Centre, Cambridge CB4 0WS (GB).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 03/063873 A1

(54) Title: USE OF 4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL)THIENO(2, 3-D)-PYRIMIDINE FOR TREATING OF URINARY INCONTINENCE

(57) Abstract: 4-(2-Fluorophenyl)-6-methyl-2-(-piperazynil)thieno[2,3-d]pyrimidine or a salt thereof is useful for the treatment of urinary incontinence.

A03

USE OF 4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL)THIENO(2,3-D-PYRIMIDINE
FOR TREATING OF URINARY INCONTINENCEField of the Invention

This invention relates to a new therapeutic use for a known compound.

5 Background of the Invention

4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride is known (see US-A-4695568) and has shown activity as an antidepressant. It has serotonin and noradrenergic reuptake blocking properties and this is thought to be the mechanism for its action as an antidepressant. The compound
10 also has 5HT-3 receptor blocking activity.

Urinary incontinence is a distressing condition which is poorly treated. It can be classified as urge (caused by overactive bladder) or stress (for example caused by prolapse of the bladder to a position which puts excessive pressure on the urethral sphincter). Some unfortunate patients have both of these types of urinary incontinence
15 which is known as mixed. Other types of urinary incontinence have been described, including functional incontinence, overflow incontinence and transient incontinence (a temporary condition due to infection or medication). Urinary incontinence can be caused by a number of disorders.

All of the drugs used for incontinence have side effect problems which often
20 result in non-compliance with treatment or a necessary withdrawal of treatment. Also they are not always effective. For stress incontinence, surgery is often the only answer although an antidepressant that is a serotonin and noradrenaline reuptake blocker, duloxetine, is showing some promise in clinical trials. Other antidepressants have also shown activity in *in vivo* models of urinary incontinence (see US-A-5744474).

25 Summary of the Invention

Surprisingly, it has been found that the known compound identified above (referred to herein as MCI-225) has activity in the treatment of urinary incontinence. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not properly been identified as being responsible for activity in
30 incontinence. Furthermore MCI-225, at doses effective in the treatment of urinary incontinence, can produce a lower incidence of some of the side-effects which are

commonly known to be associated with the clinical use of selective serotonin reuptake inhibitors, for example the production of nausea and vomiting or the induction of sexual dysfunction. It will be appreciated that any suitable form of the active principle may be used, e.g. another salt form, or a prodrug or active metabolite.

5 Description of the Invention

By means of this invention, incontinence can be treated, e.g. controlled or prevented. For this purpose, the active compound can be formulated in any suitable manner together with a conventional diluent or carrier. The active compound is preferably administered by the oral route; other suitable routes of administration include
10 sublingual/buccal, transdermal, intramuscular, intranasal, rectal, parenteral, subcutaneous, pulmonary and topical. The dose of the active agent will depend on the nature and degree of the complaint, the age and condition of the patient and other factors known to those skilled in the art. A typical daily dosage may be 0.1mg to 1000 mg.

A pharmaceutical composition containing the active ingredient may be in the form
15 of a sublingual tablet or patch. Suitable compositions for oral use include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups and elixirs. Suitable additives include sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, e.g. inert
20 diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the
25 gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated, to form osmotic therapeutic tablets for controlled release. Hard gelatin capsules may include an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin; soft gelatin capsules may include water or an oil
30 medium, for example peanut oil, liquid paraffin or olive oil.

The data on which this invention is based will now be described. In a study, using intact animals, the ability of MCI-225 to increase the tone of the urethra/internal sphincter

(a desired effect for the treatment of stress urinary incontinence) was assessed. The results show that MCI-225 is able to increase the smooth muscle tone of the lower urinary tract and will thus be of clinical utility in urinary incontinence.

Study

- 5 Female Sprague-Dawley rats (225-350g) were anaesthetised using urethane. The bladder was exposed through a midline incision into the abdomen and intravesicular pressure was recorded via a catheter inserted into the bladder. A second catheter was inserted into the bladder to allow infusion of saline using a syringe pump when required. A third catheter was inserted into the bladder and wedged into position in the neck of the
- 10 bladder with the catheter extending into the urethra. This set-up allowed constant infusion of saline into the urethra whilst urethral pressure was recorded. Changes in urethral pressure are assumed to reflect changes in urethral resistance. In each animal, electromyographic (EMG) recordings were made of urethral striated muscle activity by inserting 2 fine copper electrodes either side of the urethral opening.
- 15 Once stable, bladder and urethral pressures were recorded, the bladder was inflated by direct infusion of physiological saline into the bladder at a rate of 0.046 ml/min. This rate approximates the maximum hourly diuresis rate. Infusion into the bladder was terminated prior to evoking micturition and the bladder volume maintained. During and after saline infusion, simultaneous recordings were made of urethral perfusion pressure and
- 20 of external sphincter EMG activity. Once these parameters had stabilised, autonomic drive to the lower urinary tract was inhibited by administration of hexamethonium (10 mg/kg i.v.) and changes to urethral perfusion pressure and external sphincter EMG recorded. Decamethonium (30 mg/kg i.v.) was then added to remove striated muscle activity. In one group of animals, prior to intravesicular infusion of saline a single bolus dose of MCI-225
- 25 was administered (3mg/kg i.v.). In a second group of animals a bolus dose of vehicle was administered. The effect of MCI-225 and vehicle was determined by analysing the changes in urethral perfusion pressure and external sphincter EMG activity during and after infusion and following administration of the ganglion blocker hexamethonium and then finally decamethonium to block the striated muscle activity of the external sphincter.
- 30 Results are shown in Tables 1 and 2. They show that MCI-225 caused a rise in urethral pressure from 13 ± 1 mmHg to 23 ± 2 mmHg, an increase of 77%. The vehicle control on the other hand caused a rise in urethral pressure from 14 ± 1 mmHg to 18 ± 2

mmHg, an increase of only 29%. The rise in pressure caused by MCI-225 was statistically significant ($p=0.04$ Students t test) whereas the rise with control was not. This implies that the administration of MCI-225 increased the tone of the urethra/internal sphincter, a desired effect for the treatment of urinary incontinence.

5 Also of importance are the results seen when hexamethonium was administered to the animals. Inhibition of the autonomic nervous system with hexamethonium caused a fall in urethral perfusion pressure, and the magnitude of the drop identified the extent to which urethra/internal sphincter tone (due to autonomic nervous system activity) was contributing to outlet resistance. The drop seen in MCI-225-treated animals ($55 \pm 5\%$)
10 was greater than vehicle-treated animals ($35 \pm 7\%$). Larger falls in external sphincter activity (EUS-EMG) were seen in MCI-225-treated animals. These results imply that the administration of MCI-225 had increased the tone of urethra/internal sphincter, the desired effect for the treatment of stress urinary incontinence.

When decamethonium was administered there were some further small decreases
15 in urethral perfusion pressure; decreases from values measured before hexamethonium administration were $64 \pm 7\%$ and $44 \pm 4\%$ for MCI-225 and vehicle-treated animals respectively.

Table 1. Baseline values for mean arterial blood pressure (MAP), heart rate (HR) and urethral perfusion pressure (UP) in anaesthetized female rats.

20		<i>n</i>	MAP (mmHg)	HR (beats min ⁻¹)	UP (mmHg)
	Control	3	104 ± 3	375 ± 12	14 ± 1
	MCI-225 (3 mg kg ⁻¹)	3	105 ± 6	405 ± 15	13 ± 2

Table 2. Values of vesicular pressure (VP) and urethral perfusion pressure (UP) after
25 intravesicular infusion in anaesthetized female rats.

	<i>n</i>	VP (mmHg)	UP (mmHg)
Control	3	9 ± 2	18 ± 2
MCI-225 (3 mg kg ⁻¹)	3	8 ± 1	23 ± 2

CLAIMS

1. Use of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of urinary incontinence.
- 5 2. Use according to claim 1, wherein the salt is the monohydrate hydrochloride.
3. Use according to claim 1 or claim 2, wherein the urinary incontinence is stress urinary incontinence.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/GB 03/00374A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519 A61P13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EGUCHI JUNICHI ET AL: "The anxiolytic-like effect of MCI-225, a selective NA reuptake inhibitor with 5-HT3 receptor antagonism." PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, vol. 68, no. 4, April 2001 (2001-04), pages 677-683, XP002239887 ISSN: 0091-3057 abstract --- -/--	1-3



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

6 May 2003

Date of mailing of the international search report

20/05/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ansaldo, M

INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/GB 03/00374

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 2000 (2000-05) WU YING-LIANG ET AL: "Effects of acute and chronic administration of MCI-225, a new selective noradrenaline reuptake inhibitor with 5-HT₃ receptor blocking action, on extracellular noradrenaline levels in the hypothalamus of stressed rats." Database accession no. PREV200000291518 XP002239889 abstract & JAPANESE JOURNAL OF PHARMACOLOGY, vol. 83, no. 1, May 2000 (2000-05), pages 31-38, ISSN: 0021-5198</p> <p>---</p>	1-3
Y	<p>EP 0 467 365 A (SQUIBB & SONS INC) 22 January 1992 (1992-01-22) abstract; claims 1-9 page 2, line 49 -page 3</p> <p>---</p>	1-3
Y	<p>CHEN H I: "Evidence for the presynaptic action of 5-hydroxytryptamine and the involvement of purinergic innervation in the rabbit lower urinary tract." BRITISH JOURNAL OF PHARMACOLOGY. ENGLAND SEP 1990, vol. 101, no. 1, September 1990 (1990-09), pages 212-216, XP009010232 ISSN: 0007-1188 abstract</p> <p>---</p>	1-3
Y	<p>US 5 744 474 A (THOR KARL B) 28 April 1998 (1998-04-28) cited in the application column 3, line 36,37 column 8</p> <p>-----</p>	1-3

INTERNATIONAL SEARCH REPORT

Interr Application No

PCT/GB 03/00374

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0467365	A	22-01-1992	CA 2044854 A1	20-01-1992
			EP 0467365 A2	22-01-1992
			JP 4234328 A	24-08-1992
<hr/>				
US 5744474	A	28-04-1998	AT 201594 T	15-06-2001
			AU 679269 B2	26-06-1997
			AU 7896894 A	01-06-1995
			CA 2136120 A1	25-05-1995
			CN 1107699 A , B	06-09-1995
			CZ 9402893 A3	12-07-1995
			CZ 290573 B6	14-08-2002
			DE 69427337 D1	05-07-2001
			DE 69427337 T2	31-10-2001
			DK 654264 T3	30-07-2001
			EP 0654264 A1	24-05-1995
			ES 2157958 T3	01-09-2001
			GR 3036446 T3	30-11-2001
			HK 1013799 A1	08-02-2002
			HU 72317 A2	29-04-1996
			IL 111705 A	11-01-2001
			JP 7188003 A	25-07-1995
			NO 944456 A	26-05-1995
			PT 654264 T	28-09-2001
			RU 2152786 C2	20-07-2000
			SI 654264 T1	31-10-2001
			ZA 9409190 A	20-05-1996
<hr/>				